REMARKS

I. Support for the Amendments

Claims 1-41 were originally in the application. Claims 10-21 and 31-41 are non-elected claims withdrawn without prejudice to pursuing them in an appropriate divisional or continuation application. Applicants hereby withdraw non-elected claims 10-21 and 31-41 and cancel claims 2, 4-6, and 27, both without prejudice to the pursuit of these claims in an appropriate divisional or continuation application. Claims 1, 3, 7, 9, 23-26, 29, 42, and 43 have been amended and new claims 47-82 have been added. No new matter has been added. Claims 2, 4-6, and 27 have been canceled without prejudice to the pursuit of these claims in an appropriate divisional or continuation application.

Claims 1, 3, 7-9, 22-26, 28-30, and 42-82 are presently in the application.

Claims 1, 3, 9, 23-26, 42, and 43 were amended in part to recite the limitation of VEGF-2.

Support for amended claims 1, 3, 7, 9, 23-26, 29, 42, and 43 can be found in the original specification and claims.

Support for new claims 47-82 can be found in the original specification and claims, particularly in claims 1, 4, 7-9, 23, 24, and 26-30.

Additional support for amended claims 1, 3, 7, 9, 23-26, 29, 42 and 43 and new claims 47-82 can be found, e.g., throughout the specification and in the Examples, particularly Examples 1-7 and 11. Additional support for amended claims 1, 3, 7, 9, 23-26, 29, 42, and 43, and new claims 81 and 82 can be found, e.g., on page 14, lines 7-13. Additional support for amended claims 1, 9, 26, 43, and 44, and new claims 49-56 can be found, e.g., from page 17, line 7, to page 18, line 13. Additional support for new claims 57-61 can be found, e.g., from page 21,

line 30, to page 22, line 6; and on page 22, lines 22-24. Additional support for new claims 62-73 can be found, e.g., on page 22, lines 8-18 and lines 22-24. Additional support for new claims 74-80 can be found, e.g., from page 20, line 14, to page 21, line 28; and on page 22, lines 22-24. Additional support for amended claims 1 and 26 and for new claims 47 and 48 can be found, e.g., in Example 4.

II. Status of the Claims

Claims 1-41 were originally in the application. Claims 1-41 are subject to an election/restriction requirement, and Group I (claims 1-9 and 22-30) was elected with traverse. Claims 10-21 and 31-41 are non-elected claims hereby withdrawn without prejudice to pursuing them in an appropriate divisional or continuation application.

Claims 1, 3, 7-9, 22-26, 28-30, and 42-82 are presently in the application. Claims 2, 4-6, and 27 have been canceled without prejudice to the pursuit of these claims in an appropriate divisional or continuation application, and new claims 47-82 have been added.

III. The Drawings Have Been Accepted

The Examiner has noted that the drawings filed on 2 October 2001 have been accepted. Applicants thank the Examiner accordingly.

IV. The References in the Information Disclosure Statements

The Examiner has initialed the references cited in the Information Disclosure Statements (Forms PTO-1449) mailed on January 8, 2002, January 22, 2003, October 31, 2003, and March 3, 2004. Applicants thank the Examiner accordingly.

V. The Amendment to the Specification with Respect to the Priority Claim

The Examiner has requested amendment of the specification with respect to the claim for benefit of the provisional application as a provisional application, rather than as a continuation application. Applicants have amended the specification accordingly and respectfully submit that the application is in compliance.

VI. The Objections to the Specification are Accommodated

The Examiner has objected to the specification for the citation to the GenBank hyperlink and for the manner of citation of trademarks. Applicants have amended the specification to accommodate the Examiner's objections.

Applicants respectfully submit that the amendments to the specification place the application in condition for allowance.

VII. The Objections to Claims 4, 6, and 29 are Accommodated or Rendered Moot

The Examiner has objected to claim 4 for improper form and to claims 6 and 29 for informalities (typographical errors). Claims 4 and 6 have been canceled, and the Examiner's objections to these claims are rendered moot. Applicants have accommodated the Examiner's objection to claim 29 by amending the typographical error.

Applicants respectfully submit that the amendment to claim 29 places the application in condition for allowance.

VIII. The Rejections of Claims 1-9, 22-30, and 42-46 under 35 U.S.C. §112, First Paragraph, with Respect to Enablement are Traversed, but Rendered Moot

The Examiner has rejected claims 1-9, 22-30, and 42-46 under 35 U.S.C. §112, first paragraph, for reasons relating to enablement. Claims 2, 4-6, and 27 have been canceled and, the rejection of these claims is accordingly rendered moot. With respect to the remaining claims 1, 3, 7-9, 22-26, 28-30, and 42-46, Applicants respectfully traverse this rejection, but amendments to the claims have rendered this rejection partly moot.

The Examiner alleges:

> Claims 1-9, 22-30, and 42-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing formation of new lymphatic vessels in a mammal by administering VEGF, does not reasonably provide enablement for a method of inducing formation of new lymphatic vessels by administering fragments of VEGF. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims....
>
> The claims are drawn to methods for inducing the formation of new lymphatic vessels by administering fragments of VEGF. However, Applicants have provided no guidance as to what size fragment would be sufficient or what region of VEGF would be sufficient for achieving the formation of new lymphatic vessels. Applicants define an "effective fragment" as an "amino acid sequence that exhibits at least about 70%, preferably at least about 80% to about 95% of the lymph vessel promoting activity of the corresponding full-length protein" (see p. 17, lines 1-4 of the specification). Certain positions in a protein sequence are critical to the protein's structure/function relationship, such as various sites or regions directly involved in binding, activity, and in providing the correct three-dimensional spatial orientation of binding and active sites. One of skill in the art would not know which amino acids may be deleted from VEGF in order to yield effective fragments of VEGF. VEGF itself is alternatively spliced into at least five variants which give rise to peptides comprising 121, 145, 165, 189, and 206 amino acids. Zhang et al. teach that VEGF121 is more angiogenic and tumorigenic then the 165 and 189 isoforms (Zhang et al. (2000), *British Journal of Cancer* 83(1): 63-68). Thus, depending on the amino acid sequence of the protein, variations may occur in the activity of VEGF.
>
> Due to the large quantity of experimentation necessary to generate the fragments recited in the claims and screen the same for activity, the lack of direction/guidance presented in the specification regarding which structural features are

> required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on polypeptide structure and function, and the breadth of the claims which fail to recite any structural limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention. [Pp. 4-5.]

Applicants respectfully disagree. First, Applicants have amended the claims to read "VEGF-2," rather than "VEGF." With respect to the use of the phrase "effective fragment thereof," no undue experimentation is required by the definition on page 17, lines 1-4, because the specification also provides assay methods, which can be used to measure activity of VEGF-2 variants. Moreover, due to the amendments to claims 1 and 26, more particular fragments are claimed and a way of testing is provided that is no more than routine and does not require undue experimentation. One of ordinary skill in the art would know how to make and use the claimed invention in view of the teachings of the specification. Finally, the references cited by the Examiner with respect to 35 U.S.C. 102 show that many fragments are known in the art.

Applicants respectfully submit that claims 1, 3, 7-9, 22-26, 28-30, and 42-46 fulfill the requirements of 35 U.S.C. §112, first paragraph, with respect to the enablement requirement, and request the Examiner's reconsideration of these claims accordingly.

IX. The Rejection of Claims 1-9, 22-30, and 42-46 under 35 U.S.C. §112, First Paragraph, is Accommodated in Part, Traversed in Part, and Rendered Moot

The Examiner has rejected claims 1-9, 22-30, and 42-46 under 35 U.S.C. §112, first paragraph, for reasons relating to written description. Claims 2, 4-6, and 27 have been canceled, and the rejection of these claims is accordingly rendered moot. With respect to the remaining claims 1, 3, 7-9, 22-26, 28-30, and 42-46, Applicants respectfully traverse this rejection in part. Applicants' amendments to the claims have partly accommodated the Examiner's rejection and rendered it moot.

With respect to the written description requirement, the Examiner alleges:

....The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are drawn to a genus, i.e. a method of inducing formation of new lymphatic vessels by administering VEGF. The genus includes methods of inducing formation of new lymphatic vessels by administering fragments of VEGF. Applicants have disclosed one species, a method of administering VEGF, but have not disclosed sufficient species for the broad genus which includes administering any fragment of VEGF to induce formation of lymphatic vessels.

....The instant specification fails to provide sufficient descriptive information, such as regions of VEGF which are critical to inducing formation of lymphatic vessels. Applicants are claiming a species which has not been sufficiently described, i.e. Applicants are claiming sequences of VEGF that have not yet been identified. Only once the VEGF fragments have been generated and their functions have been determine can a person of skill in the art determine that the VEGF fragments are able to induce formation of lymphatic vessels. Thus, no identifying characteristics or properties of the instant VEGF fragments are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. Accordingly, one of skill in the art would doubt that Applicants had possession of the claimed species at the time the application was filed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acid molecules, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, the disclosure of VEGF is insufficient to describe the genus. Therefore, one of skill in the art would reasonably conclude that the disclosure

> fails to provide a representative number of species to describe and enable the genus as broadly claimed. [Pp. 5-7.]

Applicants respectfully disagree. First, Applicants have amended the claims to read "VEGF-2," rather than "VEGF." With respect to the use of the phrase "effective fragment thereof," no undue experimentation is required by the definition on page 17, lines 1-4, because the specification also provides assay methods, which can be used to measure activity of VEGF-2 variants. Again, due to the amendments to claims 1 and 26, more particular fragments are claimed and a way of testing is provided that is no more than routine and does not require undue experimentation. One of ordinary skill in the art would know how to make and use the claimed invention in view of the teachings of the specification. Finally, the references cited by the Examiner with respect to 35 U.S.C. 102 show that many fragments are known in the art.

Applicants respectfully submit that claims 1, 3, 7-9, 22-26, 28-30, and 42-46 fulfill the requirements of 35 U.S.C. §112, first paragraph, with respect to the written description requirement, and request the Examiner's reconsideration of these claims accordingly.

X. The Rejection of Claims 1-3, 5-8, 26, 29-30, and 45-46 under 35 U.S.C. §102(e) by Achen is Accommodated in Part and Rendered Moot

The Examiner has rejected claims 1-3, 5-8, 26, 29-30, and 45-46 under 35 U.S.C. §102(e) as being anticipated by Achen (U.S. Patent Application Publication 2002/0127222). Claims 2, 5, and 6 have been canceled and, the rejection of these claims is accordingly rendered moot. Applicants' amendments to claims 1, 3, 7, 9, 26, and 29 have rendered this rejection moot.

The Examiner alleges:

> Claims 1-3, 5-8, 22, 25, 26, 29-30, and 45-46 are drawn to methods for inducing formation of new lymphatic vessels in mammals by administering effective amounts of VEGF or effective fragments thereof sufficient to form new vessels in mammals. The

> VEGF may be sufficient to increase growth of new lymphatic vessels following lymphedema. The mammal being treated may be a rabbit, rodent or primate or more specifically a human patient. **Achen et al. teach administering VEGF-D or effective fragments thereof** to patients to stimulate lymphangiogenesis for the treatment or alleviation of lymphedema (see paragraph 0044 and claim 42). Thus, claims 1-3, 5-8, 26, 29-30, and 45-46 are anticipated by Achen et al. [Pp. 7-8; bold emphasis added.]

First, Applicants have amended the claims to read "VEGF-2," rather than "VEGF." Thus, the present claims are not anticipated by Achen under 35 U.S.C. §102(e). Moreover, Achen neither describes nor suggests use of VEGF-2 for inducing formation of new lymphatic vessels in a mammal, wherein the mammal has, is suspected of having, or will have lymphedema or a medical condition associated with the same in conjunction with the co-administration of at least one angiogenic protein. Similarly, Achen neither describes nor suggests use of VEGF-2 for inducing formation of new lymphatic vessels in a mammal, wherein the mammal is at risk for, is suspected of being at risk for, or will have lymphedema or a medical condition associated with the same and wherein the VEGF-2 is administered to the mammal prior to exposing the mammal to conditions conducive to damaging lymphatic vessels.

In addition, paragraph 0013 of Achen teaches away from VEGF-2 (VEGF-C) and effective fragments thereof by emphasizing that VEGF-D "is **structurally and functionally distinguished** from other members of VEGF family," as "[h]uman VEGF-D is **only 48% identical** to VEGF-C, which is the member of the family to which VEGF-D is most closely related" (paragraph 0013; bold emphasis added). (See also paragraph 0100.) As a result, the present claims also would not be obvious under 35 U.S.C. §103 in view of Achen.

Finally, the multiple injection method, as claimed in amended claims 1 and 26, is not taught by Achen. Applicants have shown that repeated administration is needed for the methods described in claims 1 and 26 (see Example 4).

Due to the cancellation of claims 2, 5, and 6 and the amendments to claims 1, 3, 7, 9, 26, and 29, Applicants respectfully submit that the present claims fulfill the requirements of 35 U.S.C. § 102(e) and request the Examiner's reconsideration of these claims accordingly.

XI. The Rejection of Claims 1-8, 22, 25-27, 29-30, 42, and 45-46 under 35 U.S.C. §102(e) by Alitalo is Accommodated in Part and Rendered Moot

The Examiner has rejected claims 1-8, 22, 25-27, 29-30, 42, and 45-46 under 35 U.S.C. §102(e) as being anticipated by Alitalo (U.S. Patent 6,730,658). Claims 2, 4-6, and 27 have been canceled and, the rejection of these claims is accordingly rendered moot. Applicants' amendments to claims 1, 3, 7, 25, 26, 29, and 42 have rendered this rejection moot.

The Examiner alleges:

> Claims 1-3, 5-8, 26 ,29-30, and 45-46 are as stated above. Claims 4, 27, and 42 are drawn to a method of administering VEGF-2 or an effective fragment thereof. Alitalo *et al.* teach administering VEGF-C (also known in the art as VEGF-2, see p. 7 in specification) to patients that are in need of lymphatic tissue growth (column 49, lines 43-49). Alitalo *et al.* teach the use of VEGF-C peptides and effective fragments thereof for the treatment of the physical loss of lymphatic vessels and lymphatic vessel occlusion (see column 5, lines 25-30 and column 9, lines 46-57). Alitalo *et al.* specifically envision treating humans suffering from such endothelial cell disorders (column 9, lines 56-57). Thus, claims 1-8, 26-27, 29-30, 42, and 45-46 are anticipated by Alitalo et al. [P. 8.]

Moreover, Alitalo neither describes nor suggests use of VEGF-2 for inducing formation of new lymphatic vessels in a mammal, wherein the mammal has, is suspected of having, or will have lymphedema or a medical condition associated with the same in conjunction with the co-administration of at least one angiogenic protein. Similarly, Alitalo neither describes nor suggests use of VEGF-2 for inducing formation of new lymphatic vessels in a mammal, wherein the mammal is at risk for, is suspected of being at risk for, or will have lymphedema or a medical condition associated with the same and wherein the VEGF-2 is administered to the mammal prior to exposing the mammal to conditions conducive to damaging lymphatic vessels. Finally, the multiple injection method, as claimed in amended claims 1 and 26, is not taught by Alitalo. Applicants have shown that repeated administration is needed for the methods described in claims 1 and 26 (see Example 4).

Due to the cancellation of claims 2, 4-6, and 27 and the amendments to claims 1, 3, 7, 25, 26, 29, and 42, Applicants respectfully submit that the present claims fulfill the requirements of 35 U.S.C. §102(e) and request the Examiner's reconsideration of these claims accordingly.

XII. The Rejection of Claims 1-6, 9, 29-30, and 42-43 under 35 U.S.C. §102(a) by Eicher is Accommodated in Part and Rendered Moot

The Examiner has rejected claims 1-6, 9, 29-30, and 42-43 under 35 U.S.C. §102(a) as being anticipated by Eicher (WO 99/49882). Claims 2 and 4-6 have been canceled and, the rejection of these claims is accordingly rendered moot. Applicants' amendments to claims 1, 3, 9, 26, 29, 42, and 43 have rendered this rejection moot.

The Examiner alleges:

> Claims 1-6, 29-30, and 42 are as stated above. Claims 9 and 43 are drawn to methods of administering VEGF-2 with at least one angiogenic protein. Eicher teaches the administration of VEGF and VEGF-c to promote new blood and lymphatic vessel formation (see p. 4). Eicher teaches that VEGF and VEGF-C act synergistically (see p. 3). Thus, claims 1-6, 9, 29-30, and 42-43 are anticipated by Eicher. [P. 8.]

Moreover, Eicher neither describes nor suggests use of VEGF-2 for inducing formation of new lymphatic vessels in a mammal, wherein the mammal has, is suspected of having, or will have lymphedema or a medical condition associated with the same in conjunction with the co-administration of at least one angiogenic protein. Similarly, Eicher neither describes nor suggests use of VEGF-2 for inducing formation of new lymphatic vessels in a mammal, wherein the mammal is at risk for, is suspected of being at risk for, or will have lymphedema or a medical condition associated with the same and wherein the VEGF-2 is administered to the mammal prior to exposing the mammal to conditions conducive to damaging lymphatic vessels. Finally, the multiple injection method, as claimed in amended claims 1 and 26, is not taught by Eicher. Applicants have shown that repeated administration is needed for the methods described in claims 1 and 26 (see Example 4).

Due to the cancellation of claims 2 and 4-6 and the amendments to claims 1, 3, 9, 26, 29, 42, and 43, Applicants respectfully submit that the present claims fulfill the requirements of 35 U.S.C. § 102(a) and request the Examiner's reconsideration of these claims accordingly.

XIII. The Rejection of Claims 1-8, 22, 25-27, 29-30, 42, and 45-46 under 35 U.S.C. §102(a) and §102(e) by Hu is Accommodated in Part and Rendered Moot

The Examiner has rejected claims 1-8, 22, 25-27, 29-30, 42, and 45-46 under 35 U.S.C. §102(a) and §102(e) as being anticipated by Hu (U.S. Pat. 6,040,157). Claims 2, 4-6, and 27 have been canceled and, the rejection of these claims is accordingly rendered moot. Applicants' amendments to claims 1, 3, 7, 25, 26, 29, 42, and 43 have rendered this rejection moot.

The Examiner alleges:

> Claims 1-8, 22, 25-27, 29-30, 42, and 45-46 are as stated above. Hu *et al.* teach methods of administering VEGF-2 polypeptides or biologically effective fragments thereof for treating the loss of lymphatic vessels, occlusions of lymphatic vessels, and lymphangiomas (see column 30, lines 16-20 and column 38, lines 33-36). Hu *et al.* teach VEGF-2 may be used to treat primary lymphedemas, such as Milroy's disease and Lymphedema precox, and secondary lymphedemas (see column 38, line 56 through column 39, line 7). Thus, claims 1-8, 22, 25-27, 29-30, 42, and 45-46 are anticipated by Hu *et al.* [P. 8.]

Applicants respectfully submit that Hu neither describes nor suggests use of VEGF-2 for inducing formation of new lymphatic vessels in a mammal, wherein the mammal has, is suspected of having, or will have lymphedema or a medical condition associated with the same in conjunction with the co-administration of at least one angiogenic protein. Similarly, Hu neither describes nor suggests use of VEGF-2 for inducing formation of new lymphatic vessels in a mammal, wherein the mammal is at risk for, is suspected of being at risk for, or will have lymphedema or a medical condition associated with the same and wherein the VEGF-2 is

administered to the mammal prior to exposing the mammal to conditions conducive to damaging lymphatic vessels. Finally, the multiple injection method, as claimed in amended claims 1 and 26, is not taught by Hu. Applicants have shown that repeated administration is needed for the methods described in claims 1 and 26 (see Example 4).

Due to the cancellation of claims 2, 4-6, and 27 and the amendments to claims 1, 3, 7, 25, 26, 29, 42, and 43, Applicants respectfully submit that the present claims fulfill the requirements of 35 U.S.C. § 102(a) and § 102(e) and request the Examiner's reconsideration of these claims accordingly.

CONCLUSION

It is believed that all outstanding rejections have been addressed by this submission and that all the claims are in condition for allowance. If discussion of any amendment or remark made herein would advance this important case to allowance, the Examiner is invited to call the undersigned as soon as convenient.

In view of the foregoing amendments and remarks, the present application is respectfully considered in condition for allowance. An early reconsideration and notice of allowance are earnestly solicited.

Applicants hereby request a two-month extension of time for the Amendment and submit the requisite fee herewith. If, however, a petition for an additional extension of time is required, then the Examiner is requested to treat this as a conditional petition for an additional extension of time. Although it is not believed that any fee is required, in addition to the fee submitted herewith, to consider this submission, the Commissioner is hereby authorized to charge our deposit account no. 04-1105 should any fee be deemed necessary.

Respectfully submitted,

Date: October 20, 2004

Kathryn A. Piffat, Ph.D. (Reg. No. 34,901)
Intellectual Property Practice Group of
EDWARDS & ANGELL, LLP
P.O. Box 55874
Boston, MA 02205
(617) 439-4444
(617) 439-4170 (fax)

Customer No. 21874